REMARKS

Claims 1-11 and 13-52 are pending.

Claims 1-11, 13-17, 25, 44, and 48-52 are under examination (currently restricted to species A, C, H, and S of record), claims 18-24, 26-43, and 45-47 having been withdrawn by the Examiner as being drawn to non-elected species.

Applicants thank the Examiner for *withdrawal* of particular prior objections (claim 2), and prior rejections of: claims 1-10 and 48 under 35 U.S.C. § 102(b) as being allegedly anticipated by Tornaletti et al.; claims 1, 2, 10-11, 49-50, and 52, under 35 U.S.C. § 103(a) as being allegedly obvious over Tornaletti et al. (*Oncogene*, 10:1493-1499, 1995), in view of Gaasterland et al. (*Nature Genetics*, 24:204-206, March 2000); and claims 1-2, 6-7, 11-17, 44, and 48-50, under the doctrine of nonstatutory obviousness-type double patenting, over claims 1-2, 4-5, 9-15, 38, and 42-44 respectively of copending application 10/106,269, based on Applicants' responsive claim amendments and rebuttal arguments.

Applicants thank the Examiner for indicating that claims 25, 44, and 51 are free of the prior art.

Applicants acknowledge the Examiner's new objection to claims 1 and 10. Applicants have made responsive amendments to obviate these objections, and conforming amendments have been made to claim 11.

Applicants acknowledge the Examiner's new rejection of claims 13-17, 25, 44, and 51, under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants have responsively amended the claim 13 to obviate this rejection.

Applicants acknowledge the Examiner's new rejection of claims 1, 2, 10-11, 49-50, and 52 under 35 U.S.C. § 103(a) as being allegedly obvious over Tornaletti et al. (*Oncogene*, 10:1493-1499, 1995), in view of Laird et al. (US PGPub 2004/0033490, 19 February 2004), and in view Gaasterland et al. (*Nature Genetics*, 24:204-206, March 2000), and of claims 13-17 under 35 U.S.C. § 103(a) as being allegedly obvious over Tornaletti et al., in view of Laird et al., in view Gaasterland et al., and further in view of Curtis et al. (Annals in Human Genetics, 65:95-107, 2001). Applicants respectfully traverse these rejections.

No new matter has been added.

Formalities

Status Identifier. The status identifier for claim 17 has been corrected as requested by the Examiner, and now indicates "Original." Applicants thank the Examiner for pointing this out.

Claim Objections

The Examiner has objected to claim 1 in view of recitation of "each pair of classes or pair or unions the at least two… ." Applicants have amended the claim to recite "each pair of classes or pair of[[or]] unions the at least two…" to obviate this objection.

The Examiner has objected to claim 10, because claim 10 allegedly is of improper form for failing to further limit the subject matter of a previous claim. Applicants have responsively amended claim 10 to recite "wherein step e)[[d]]) is performed so as to select pairs of unions of classes from the at least ~~divide the biological samples in~~ two disjunct phenotypic classes of interest" to obviate this rejection. Conforming amendments have been made to claim 11, which not recites "method as recited in claim 10, further comprising performing, in j), the epigenetically-based prediction of the pairs of unions of ~~at least two phenotypic~~ classes of interest using a machine learning classifier." Support for the amendments is found in claim 1 and as previously cited of record, and amended claim 10 further limits claim 1 from which it depends.

Applicants, therefore, respectfully request withdrawal of these objections.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 13-17, 25, 44, and 51, under 35 U.S.C. § 112, second paragraph, as being indefinite in view of the inadvertent recitation, in claim 13, of "selection step

of g)." Applicants have amended claim 13 to recite the intended "selection step of h)" to obviate this rejection.

Applicants, therefore, respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 103

***Tornaletti**, in view of **Laird** and in view of **Gaasterland**:*

The Examiner has newly rejected claims 1, 2, 10-11, 49-50, and 52, under 35 U.S.C. § 103(a) as being allegedly obvious over Tornaletti et al. (*Oncogene*, 10:1493-1499, 1995), in view of Laird et al. (US PGPub 2004/0033490, 19 February 2004), and in view Gaasterland et al. (*Nature Genetics*, 24:204-206, March 2000).

Specifically, the Examiner recites Applicants' claim elements and states that Tornaletti teaches Applicants' method step through defining and analyzing an initial set of epigenetic features of interest, but fails to teach the step of predicting phenotypic classes of interest from epigenetic data sets (step "h)" of Applicants' claim 1), additionally fails to teach defining new epigenetic features of interest (step "i)" of Applicants' claim 1), and further fails to teach use of machine learning classifier to aid in predicting phenotypic information from epigenetic properties (step "j)" of Applicants' claim 1). The Examiner states, however, that Laird et al. discloses prediction of esophageal adendocarinoma from epigenetic features of interest (step "h)" of Applicants' claim 1) and that claims 6 of Laird further teaches defining a new set of epigenetic features of interest (step "i)" of Applicants' claim 1), but that neither Tornaletti nor Laird teach use of machine learning classifiers to aid in the process (step "j)" of Applicants' claim 1). Nonetheless, the Examiner states that Gaasterland et al. teaches a supervised computer-learning method using support vector machines to train a "classification machine" to recognize new genes that are similar in expression pattern to groups of genes that are similar in expression pattern to

groups of genes known to be co-regulated, and potentially predict gene function from expression data.

Applicants' Traversal:

Applicants respectfully traverse the Examiner's obviousness rejection, based on the fact that no *prima facie* case of obviousness is supportable in view of the asserted references alone or in combination, because **(a)** there is no suggestion or motivation embodied in the asserted art alone or in combination, even in view of knowledge generally available to one of ordinary skill in the art, to arrive at Applicants' invention, and **(b)** even if there were, there is no reasonable expectation of success based thereon where the references fundamentally *teach away* from the present invention, and **(c)** the references do not, in fact, teach all the claim limitations, and further teach elements that would preclude provision of the presently claimed subject matter.

APPLICABLE LAW. Under KSR v. Teleflex, application of the TSM test is valid provided that such application does not require an overly rigid or explicit application of the asserted prior art. Accordingly, as already stated in the record, and in keeping with KSR, to establish a *prima facie* case of obviousness there must be: (i) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (POSITA), to modify the reference or to combine reference teachings; (ii) a reasonable expectation of success; and (iii) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and knowledge generally available to POSITA, and not based on Applicants' disclosure (*In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); and see MPEP §§ 2143-2143.03). Therefore, to support a conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of

reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Moreover, there can be no reasonable expectation of success where the art, alone or in combination, *teaches away* from the invention.

Analysis:

Tornaletti

The Examiner's reliance on Tornaletti is improper and misplaced, because the Examiner has fundamentally misconstrued Tornaletti. This is obvious from a review of the Abstract alone. The abstract states that "we found that the p53 sequences along exons 5-8 were completely methylated at every CpG site, including 46 different sites on both DNA strands. This methylation pattern is tissue-independent suggesting that tissue-specific methylation does not contribute to the differential mutation patterns seen in tumors. The occurance of mutational hotspots at specific CpG sites is not related to selective methylation of only a subset of CpGs but may rather depend on a selection bias for particular amino acid changes. Our results are inconsistent with theories that mutations in tumors with high CpG mutation rates, like colon cancer, are caused by spontaneous demaination of 5-methylcytosine… ."

Therefore, not only does Tornalettie not teach the use of epigenetic analysis to practice the claimed methods, Tornalettie actually fundamentally ***teaches away*** from applicants claime invention, and particularly *teaches away* from the use of epigenetic features to practice Applicants' steps h)-j). Therefore, there is certainly no motivation, as urged by the Examiner, to combine Tornaletti with any other of the Examiner's asserted alleged prior art references, and there would be no reasonable expectation of success, based on any such combination.

Laird

As recognized by the Examiner, neither Tornaletti nor Laird teach use of machine learning

classifiers to aid in the process (step "j)" of Applicants' claim 1). Moreover, while the Examiner states that Gaasterland et al. teaches a supervised computer-learning method using support vector machines to train a "classification machine" to recognize new genes that are similar in expression pattern to groups of genes that are similar in expression pattern to groups of genes known to be co-regulated, and potentially predict gene function from expression data, this is a completely different application from that presently claimed as discussed below.

Gaasterland

Gaasterland may teach SVMs, but they do so only in the context of recognizing new genes that are similar in expression pattern to groups of genes known to be co-regulated. Application of SVM premised on a known expression class ("genes known to be co-regulated") does not reasonably teach application of SVM in the ***epigenetic*** context as presently claimed. There is no suggestion in any of the asserted alleged prior art referencesm, alone or in combination, to use SVM methods for ***epigenetic*** prediction analysis, based on it prior application in the fundamentally different context of similarly expressed and/or co-regulated genes. Moreover, the Examiner, aside from a conclusory statement, has articulated no reason why a person of skill in the art would be motivated to combine the three different references, as urged by the Examiner, with a reasonable expectation of success. Applicants respectfully contend that this amounts to inappropriate hindsight.

Tornaletti**, in view of **Laird**, in view of **Gaasterland** and in view of **Curtis

The Examiner has additionally newly rejected claims 13-17 under 35 U.S.C. § 103(a) as being allegedly obvious over Tornaletti et al. (*Oncogene*, 10:1493-1499, 1995), in view of Laird et al. (US PGPub 2004/0033490, 19 February 2004), and in view Gaasterland et al. (*Nature Genetics*, 24:204-206, March 2000), Laird and Gassterland as applied above, and further in view

of Curtis et al. (Annals in Human Genetics, 65:95-107, 2001).

Specifically, the Examiner states that Tornaletti, Laird, and Gaasterland teach elements of the inventions of claims 13-17, except ranking of epigenetic feature sets using cardinalities. However, the Examiner states that Curtis et al. teaches the study of SNPs and how using the epigenetic properties of SNPs can be used to predict disease (citing the Abstract of Curtis) this limitation.

Applicants respectfully traverse this rejection, because Curtis et al. does not, as urged by the Examiner, teach use of *epigenetic* properties to predict disease, and does not rank epigenetic properties in predicting disease. Rather, Curtis studies haplotypes (not epigenetic changes) associated with particular SNPs (single nucleotide polymorphism), and thus uses neural network methods to study convention DNA sequence changes (SNPs). Therefore, while Curtis may arguable (but see below) define feature selection criteria for SNPs, there is no teaching of defining feature selection criteria for epigenetic features (e.g., cytosine methylation)—which are fundamentally different than SNPs. There is, therefore, no teaching or suggestion in the asserted references, alone or in combination, to use ranking of epigenetic features comprising definition of an epigenetic feature selection criteria.

More specifically, the teachings of Curtis do not encompass epigenetic features or methylation, because the Curtis teachings are limited to artificial (*i.e.*, virtual) data sets comprising virtual single nucleotide polymorphisms (SNPs) (Curtis at page 99, first column; "then for each marker a single mutation event was modeled... ."). Generations of virtual recombination were then made and a disease mutation introduced, followed by further virtual recombination to diminish linkage disequilibrium between the disease and SNP marker loci (the disease locus having been placed at a fixed map position relative to the SNP marker loci) and produce a dataset with varying degrees of linkage disequilibrium between the disease and marker loci (Curtis at page

99, second column).

Contrary to the Examiner's urging, Curtis does not teach use neural networks to classify between disease and multiple marker genotypes in the sense of the presently claimed invention. Rather, Curtis teaches that a "useful increase in power can be obtained in a [simulated] case controlled association study by using an artificial neural network to analyse data from multiple SNPs simultaneously" (page 105, second column). That is, Curtis teaches that, compared to analysis using single marker tests (either using just one single marker test or a combination of single marker tests), simultaneous analysis of multiple (*e.g.*, 2, 3, or 4) linked markers increases the power (or frequency of tests showing an association) by, for example, 10% (*Id*). Contrary to the Examiner's urging, the data of Table 4 (cited by the Examiner) does not in fact show the results in Curtis are ranked according to linkage to an inflicted mutation over the course of many generations. Significantly, the "results" in Tables 3 and 4 do not show ranking of genetic (much less epigenetic) features in the sense of the present invention. Rather, the results, as discussed by Curtis in detail (beginning in the first column of page 104 and extending through the first column of page 105) illustrate, for each row of the table, the enhanced utility ("Overall test" column) of combining the neural network analysis ("Neural network" column) with the single marker test ("Single marker test" column). The Table also show that the extent of enhancement increases, relative to the single marker test, as one proceeds in the comparison from the use of one marker SNP mutation ("1" in the "Number of mutations" column) to two ("2" in the "Number of mutations" column), three ("3" in the "Number of mutations" column), or four ("4" in the "Number of mutations" column) SNP mutations. Therefore, there is no ranking of the different SNPs in the sense of the presently claims selection and ranking of epigenetic features. Moreover, as stated above, even if there were, the simulated data of Curtis relating to virtual SNP analysis (i.e., virtual genetic analysis) do not encompass epigenetic analysis including methylation

analysis. The linkage and linkage disequilibrium analysis of Curtis is based on the utility of genetic chromosomal map linkage, and feature selection is, therefore, limited to map linkage as recognized by the Examiner. Such is not the case for the presently claimed epigenetic features.

Therefore, while Curtis, as construed by the Examiner may teach use of neural networks as machine learning classifiers, Curtis, alone or in combination with any of the other of Examiner's asserted art does not teach or otherwise reasonably suggest, the presently claimed method of identifying and selecting relevant epigenetic features to deduce phenotypic properties in mammalian cells or tissue. None of the references, alone or in combination, teach the presently claimed methods of selection of relevant epigenetic features to predict phenotypic disjunct phenotypic classes in mammalian cells or tissues.

Moreover, as stated above, Gaasterland may teach SVMs, but they do so only in the context of recognizing new genes that are similar in expression pattern to groups of genes known to be co-regulated. Application of SVM premised on a known expression class ('genes known to be co-regulated') does not reasonably teach application of SVM in the ***epigenetic*** context as presently claimed.

Applicants, therefore, respectfully request withdrawal of these obviousness rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully requests allowance of the amended claim set provided herein above. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Respectfully submitted,

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